Title

Neuromuscular Electrical Stimulation May Attenuate Muscle Proteolysis after Cardiovascular Surgery: A Preliminary Study

Authors

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Abbreviations and Acronyms

NMES=neuromuscular electrical stimulation

eGFR=estimated glomerular filtration rate

3-MH=3-methylhistidine

POD=postoperative day

MVC=maximal voluntary contraction

Cre=creatinine

KEIS=knee extensor isometric strength

IL-6= interleukin-6

Abstract

Objective: To explore the efficacy of postoperative neuromuscular electrical stimulation (NMES) on muscle protein degradation and muscle weakness in patients after cardiovascular surgery.

Methods: Sixty-one patients underwent NMES daily from postoperative days (PODs) 1 to 5 in addition to postoperative mobilization program (NMES group), and 41 patients underwent postoperative mobilization program only (non-NMES group). The primary outcome was the concentration of 3-methylhistidine (3-MH) in 24-h urine corrected for urinary creatinine content (3-MH/Cre) from PODs 1 to 5. The secondary outcomes were knee extensor isometric strength (KEIS) and handgrip strength at POD 7.

Results: Baseline characteristics such as age, sex, preoperative body mass index, hemoglobin, handgrip strength, KEIS, surgery type, cardiopulmonary bypass time, and immediate post-operative interleukin-6 were not different between the groups. Urinary 3-MH/Cre was significantly increased in both groups. However, urinary 3-MH/Cre in the NMES group peaked earlier compared with that in the non-NMES group. KEIS at POD 7 was significantly higher in the NMES group (median [interquartile range], 0.40

kg/weight [0.33–0.45] in the NMES group vs 0.23 kg/weight [0.15–0.36] in the non-NMES group; $p < 0.01$). Handgrip strength at POD 7 was also significantly higher in the NMES group (median [inter-quartile range], 32 kg [24.5–35.3] in the NMES group vs 24 kg [16.0–30.0] in the non-NMES group; $p < 0.01$).

Conclusions: This study demonstrated that NMES might attenuate skeletal muscle protein degradation and muscle weakness after cardiovascular surgery. A cause–effect relationship between NMES and functional preservation would be a future challenging issue.

Central message

Neuromuscular electrical stimulation reduced muscle proteolysis and preserved muscle strength in patients after cardiovascular surgery.

Perspective Statement

Muscle protein catabolism after cardiovascular surgery induces postoperative muscle weakness and functional decline, for which no preventive tool has been established. Our study demonstrated the possibility of NMES to attenuate muscle protein degradation and muscle weakness in

patients after cardiovascular surgery. These data provides a rationale for application of NMES in postoperative rehabilitation.

INTRODUCTION

Surgical operation stress induces loss of muscle mass due to dysregulation in protein metabolism[1,2]. Under this condition, protein degradation is accelerated while synthesis is suppressed, leading to a net loss of muscle protein. The concurrent reduction in muscle strength causes long-term impairments such as persistent muscle weakness[3,4]. Currently, Iida et al. reported that the cumulative urinary excretion of 3-methylhistidine (3-MH) in patients within 5 days after cardiac surgery was associated with immediate postoperative interleukin-6 (IL-6) level and postoperative muscle weakness[5]. 3-MH is a product of the methylation of peptide-bound histidine in actin and myosin and is released to the free amino acid body pool upon muscle protein breakdown[6]. Because 3-MH is not reused for muscle protein synthesis or oxidized for energy[7], the urinary 3-MH has been recognized as an index of muscle proteolysis rate[6,8]. In addition, IL-6 is traditionally considered as a marker for surgical stress[9,10]. Therefore, the prevention of muscle proteolysis induced by surgical stress at the early postoperative phase may be a potential intervention for preservation of skeletal muscle strength after cardiovascular surgery.

Because immobilization, even of short duration, is an important stimulus of muscle protein degradation[11], promoting muscle activity is widely recognized as a countermeasure against muscle protein degradation. In the early postoperative phase after cardiovascular surgery, however, patients often have difficulties to produce sufficient muscle contractions due to their hemodynamic instabilities. Instead, neuromuscular electrical stimulation (NMES) can safely induce sufficient muscle activity without patient's volitional efforts even immediately after cardiovascular surgery[12]. However, data regarding the effect of postoperative NMES on skeletal muscle degradation (or weakness) in patients undergoing cardiovascular surgery have been scarce.

This study, therefore, aimed to explore the efficacy of postoperative NMES on muscle protein degradation and muscle weakness in patients after cardiovascular surgery.

MATERIALS AND METHODS

Participants and data collection

Adult patients who were scheduled for elective major cardiovascular surgery (coronary artery bypass, valvular, thoracic aorta, or combined surgery) in Nagoya University Hospital and Kainan Hospital were consecutively included. Exclusion criteria were chronic renal failure (estimated glomerular filtration rate, eGFR < 30 ml/min/1.73 m^2), peripheral arterial disease (Fontaine classification ≥ III), psychiatric disease, neuromuscular disease, dementia (Mini-Mental State Examination < 18 points), intubation more than 24 h after surgery, and reoperation. Chronic renal failure of eGFR < 30 ml/min/1.73 m^2 was excluded because of uncertainty of measured urinary 3-methylhistidine (3-MH), a marker of myofibrillar protein degradation[13,14]. Patients who withdrew from the postoperative rehabilitation program and/or NMES were also excluded. Informed consent was obtained from each patient as approved by the Ethics Review Committee of the Nagoya University Graduate School of Medicine (approval number: 1272). This study was registered in the University Hospital Medical Information Network Center (registration number: UMIN000020221).

The following preoperative clinical data were collected from the

patient's clinical record: age, sex, body mass index (BMI), and serum hemoglobin level. The intraoperative variables recorded included the type of surgical procedure (coronary bypass, valvular, thoracic aorta, or combined surgery), cardiopulmonary bypass (CPB) time, and cross clamp time. Serum IL-6 immediately after surgery was assessed in both groups. We obtained patients' blood samples from a peripheral artery 4 h after surgery to measure IL-6. Each sample was centrifuged at 2000 ×*g* for 10 min, and the serum was collected in to small SRL vials (SRL, Inc. Tokyo, Japan) and frozen to −80°C for later analysis. The IL-6 level was measured using an automated chemiluminescent enzyme immunoassay system (SRL, Inc. Tokyo, Japan). Data for IL-6 were log-converted (natural logarithm) because of the skewed distribution.

Study design

This study was conducted as a prospective, observational study. The patients from Nagoya University Hospital underwent a postsurgical rehabilitation program with NMES intervention from postoperative days (PODs) 1 to 5, and the patients from Kainan Hospital underwent

73 postsurgical rehabilitation program only.

74

75 *Intervention*

76 The patients from Nagoya University Hospital underwent NMES on the
77 bilateral quadriceps femoris and triceps surae daily from PODs 1 to 5 (5
78 sessions). During stimulation, the self-adhering surface electrodes (62 × 62
79 mm) were bilaterally positioned on the vastus lateralis, vastus medialis,
80 and triceps surae after cleaning the skin[12]. The waveform of NMES was a
81 symmetric, biphasic square wave. The stimulator was configured to deliver
82 a direct electrical current for 0.4 s followed by a pause that lasted 0.6
83 seconds. Pulse groups consisting of 10 impulse trains were delivered for
84 each muscle at 30-s intervals during the session. Duration of the session
85 was 30 to 60 min. The intensities of NMES were set to induce 10% and 20%
86 of maximal voluntary contraction (MVC), and the repetitions of
87 10%−10%−20% MVC were set throughout the session. A video of the NMES
88 was shown in Appendix 1. Daily NMES intervention started from POD 1.
89 The safety of this NMES protocol in patients immediately after
90 cardiovascular surgery has been reported elsewhere[12].

Patients in both groups underwent the postoperative mobilization program based on the guidelines of the Japanese Circulation Society under the supervision of a physical therapist (see Appendix 2).

Outcomes

The primary outcome in this study was time trend of the 3-MH concentration in 24-h urine corrected for urinary creatinine (Cre) content (3-MH/Cre) after surgery. The ratio of 3-MH to urinary creatinine was used for normalizing the data for lean body mass differences among patients. Collection of 24-h urine samples started at operative time and continued until POD 5. Urine was collected during 24 h and stored into bottles containing hydrochloric acid to avoid bacterial hydrolysis of urea. At the end of the daily urine collection, we gathered a urine sample from the pooled urine after immixture of the collected urine and stored at −80°C until processing. The 3-MH concentration was determined by high performance liquid chromatography[15] (SRL, Inc. Tokyo, Japan). The value of 3-MH and Cre in urine samples was multiplied by the 24-h urine volume to produce a value for daily 3-MH/Cre excretion.

The secondary outcomes were knee extensor isometric strength (KEIS) and handgrip strength. Both muscle strengths were measured the day before surgery (baseline) and POD 7. KEIS was measured by using an isometric dynamometer (μTas F-1; ANIMA Corp. Tokyo, Japan)., Patients sat in a chair with their hips and knee at 90° to measure KEIS. Their shin was strapped into a cuff, and they performed three maximal isometric contractions against a fixed resistance for each leg with a 3-min interval. During measurement, identical verbal encouragement was given, and force generated was measured in kilogram force. The highest value among three measurements was selected for analysis[16,17]. Handgrip strength was measured by using a JAMAR dynamometer (Sammons Preston, Rolyon, Bolingbrook, IL) set at the second grip position[18]. Measurements were made thrice on the non-dominant hand, and the highest value (in kg) was selected for analysis[16]. An image of the measurement of both muscle strengths is shown in Appendix 3. Both muscle strengths were measured by well-trained physical therapists who showed good test–retest reliability (intra-class correlation coefficients of >0.85).

Statistical analysis

We used the Wilk–Shapiro test to assess the normality of distribution of the data. Continuous variables were presented as mean±SD or median (inter-quartile range) in cases of non-normal distribution. Categorical data were reported as percentages. Group baseline characteristics were compared using *t*-test (or Mann–Whitney *U* test) for continuous variables and chi-square test for categorical variables. To assess the effect of NMES on urine 3-MH/Cre level from PODs 1 to 5, we used linear mixed models for repeated measurement. Fixed effects of interest were group (NMES/non NMES), time (postoperative days), and interaction between group and time. In addition, since the urine 3-MH/Cre level on POD1 varied between the groups, we used the value on POD1 as a covariate. Between-group and within-group comparisons for muscle strength parameters were performed using Mann–Whitney *U* test and Wilcoxon test, respectively. A p value <0.05 was considered statistically significant. All analyses were calculated using SPSS ver 16.0 (SPSS Inc., Chicago, Ill., USA).

RESULTS

Study participants

This study included 68 and 41 patients from Nagoya University Hospital and Kainan Hospital, respectively (Figure 1). No differences were found in the baseline characteristics between the groups, except for the cross clamp time (Table 1). In addition, although immobilization after surgery is an important stimulus for muscle proteolysis[11], days from surgery to initial mobilization were not significantly different between the groups.

3-MH/Cre

Time course of urinary 3-MH/Cre from PODs 1 to 5 is shown in Figure 2. Urinary 3-MH/Cre level peaked on POD 3 in the NMES group, whereas the level showed a sustained increase until POD 4 in the non-NMES group. Significant main effect for time ($F = 173.7$, $p < 0.01$) and group × time interaction ($F = 12.1$, $p < 0.01$) were found by using linear mixed models for repeated measurement. In contrast, the main effect for group was not significant ($F = 1.01$, $p = 0.31$).

Change in muscle strength

Change in KEIS from baseline to POD 7 was shown Figure 3. KEIS decreased significantly from baseline to POD 7 in both groups. The value at POD 7 in the NMES group was, however, significantly higher than that in the non-NMES group (median, 0.40 [0.33−0.45] kg/weight vs median, 0.23 [0.16−0.36]; $p < 0.01$). Handgrip strength also reduced from baseline to POD 7 in both groups (Fig. 4). The value at POD7 in the NMES group was, however, significantly higher than that in the non-NMES group (median, 32.0 [24.5−35.3] kg vs median, 25.0 [16.0−30.0]; $p < 0.01$).

DISCUSSION

The present findings support our hypothesis that NMES immediately after cardiovascular surgery is effective in reducing sustained elevation of muscle protein degradation and preserving muscle strength. To the best of our knowledge, this is the first study that demonstrates the possibility of NMES to attenuate postoperative muscle protein degradation and muscle weakness in patients after cardiovascular surgery.

The value of urinary 3-MH/Cre peaked significantly earlier in the

NMES group than in the non-NMES group. Ninety percent of the whole body protein bound to 3-MH is present in actin and myosin of the skeletal muscle[19]. Using the ratio to urinary creatinine normalizes the data for lean body mass differences among patients. Iida et al. reported that preoperative handgrip strength, BMI, hemoglobin, CPB time, and IL-6 level 4 h after surgery are independent predictors of the amount of 3-MH/Cre after cardiovascular surgery[20]. In this study, these variables were not significantly different between the groups. The results in this study, therefore, suggest that NMES may attenuate the sustained elevation of muscle proteolysis after cardiovascular surgery. Our results correspond with those observed in previous studies[21,22]. In an early study involving intensive care unit patients[21], NMES has been reported to decrease 3-MH excretion. In their study[21], however, all participants underwent NMES at least 8 days after hospitalization, when the level of metabolic stress would be low. The present study demonstrated the preventive effect of NMES on the elevation of 3-MH/Cre levels within 5 days after cardiovascular surgery, suggesting that NMES can reduce muscle proteolysis even in patients in a hypercatabolic state. Another study has reported that postoperative NMES

199 reduced muscle protein degradation in patients immediately after
200 abdominal surgery[22]. Although they showed that NMES attenuated the
201 activity of the ubiquitin–proteasome system[22] which is the main pathway of
202 protein degradation in catabolic situations[23,24], it remains unclear whether
203 this molecular biologic alteration actually leads to measurable change in
204 muscle strength. Our results add to the evidence that reduction in muscle
205 proteolysis induced by NMES were accompanied by preservation of muscle
206 strength. The mechanism of the reduction in 3-MH/Cre levels induced by
207 NMES remains unclear. As noted above, because the ubiquitin–proteasome
208 pathway physiologically plays an important role in protein degradation, we
209 assume that the possible mechanisms of the reduction in 3-MH/Cre levels
210 induced by NMES include suppression of the ubiquitin–proteasome
211 pathway.

212 KEIS decreased after surgery in both groups. However, KEIS at
213 POD 7 in the NMES group was significantly higher compared with that in
214 the non-NMES group, whereas no difference was found in the baseline
215 value between the groups. In the non-NMES group, comparable levels of
216 reduction were observed in KEIS (35.1%) and handgrip strength (30.2%) on

POD 7. In contrast, the reduction in KEIS, which were the target muscles of NMES, was 5.3% in the NMES group, whereas handgrip strength decreased by 14.9%. NMES implemented for more than 4 weeks has been reported to improve quadriceps muscle strength in stable patients with chronic obstructive pulmonary disease[17,25] and chronic heart failure[16,26]. In this study, NMES for less than 1 week (5 days) preserved quadriceps muscle strength of patients in a hypercatabolic state immediately after cardiovascular surgery. The results of this study suggest that, even in short-term, NMES intervention immediately after cardiovascular surgery might be effective in preventing postoperative muscle weakness. One explanation about the mechanism for preservation of muscle strength could be the reduction in myofibrillar degradation observed in the NMES group. Other mechanisms may include maintaining the stimulus of protein anabolism through insulin-like growth factor 1 excretion[27] because the NMES used in our study induced 20% of MVC, wherein most previous NMES could not achieve. In addition, a previous study reported that the increases in muscle strength after NMES for less than 4 weeks were accounted for the neural adaptations without muscle hypertrophy in

235 healthy young adults[28]. Further studies will be needed to clarify the
236 mechanisms for preservation of skeletal muscle strength induced by NMES
237 under the hypercatabolic state.

238 Interestingly, handgrip strength was also preserved in the NMES
239 group compared with the non-NMES group, whereas stimulation was only
240 applied to the lower extremity muscles. NMES implemented to the
241 unilateral leg has been reported to increase muscle strength in the
242 contralateral, non-stimulated leg[29,30]. In addition, a previous study reported
243 that NMES improved the sum score of the upper and lower extremity
244 muscle strength in critically ill patients[31]. The spread effect of NMES on
245 non-target muscles should be explored in future studies.

246 The present study has several limitations. The main limitation of
247 this study was the absence of randomization. In this study, NMES
248 intervention was split between two different hospitals. This practical choice
249 could have led to some potential bias. Cross clamp time in the NMES group
250 was actually shorter than that in the non-NMES group. However, patient
251 characteristics, which have been reported as predictive factors for
252 postoperative muscle proteolysis[20], were not different between the groups.

In addition, postoperative early mobilization protocol during the study period was similar in the two hospitals (see Appendix 2). Therefore, the risk of bias in this study would be low. Another limitation was the unblinded testers of muscle forces. This might lead to measurement bias that is usually avoided by methodology. Although identical encouragement was used in the pre- and post-operative measurements, and the maximal force value was accepted from the three successive measurements performed by the patients, we assume that the results of muscle force in this study still have a possibility to overestimate the effect of NEMS. To clarify this, a blinded randomized controlled trial focused on the efficacy of NEMS on postoperative muscle degradation and force reduction will be needed. Nevertheless, the findings of this study provide fundamental data regarding the possibility of NMES to overcome postoperative skeletal muscle hypercatabolism and, in turn, muscle weakness.

CONCLUSIONS

This study was the first exploratory research suggesting an anticatabolic effect of NMES in patients immediately after cardiovascular surgery. The findings of this study provide a rationale, not only for a larger blinded randomized controlled trial, but also for a study that would explore who should be prescribed with NMES for postoperative functional preservation after cardiovascular surgery. A cause–effect relationship between NMES and functional preservation would be a future challenging issue.

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References

1. Biolo G, Toigo G, Ciocchi B, Situlin R, Iscra F, Gullo A, et al. Metabolic response to injury and sepsis: changes in protein metabolism. *Nutrition.* 1997;13(9 Suppl):52S–57S.

2. Caso G, Vosswinkel JA, Garlick PJ, Barry MK, Bilfinger T V, McNurlan MA. Altered protein metabolism following coronary artery bypass graft (CABG) surgery. *Clin Sci (Lond)* . 2008;114(4):339–46.

3. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med.* 2003;348(8):683–93.

4. Watters JM, Clancey SM, Moulton SB, Briere KM, Zhu JM. Impaired recovery of strength in older patients after major abdominal surgery. *Ann Surg.* 1993;218(3):380-90–3.

5. Iida Y, Yamazaki T, Kawabe T, Usui A, Yamada S. Postoperative muscle proteolysis affects systemic muscle weakness in patients undergoing cardiac surgery. *Int J Cardiol.* 2014;172(3):595–597.

6. Long CL, Birkhahn RH, Geiger JW, Betts JE, Schiller WR, Blakemore WS. Urinary excretion of 3-methylhistidine: an assessment of muscle protein catabolism in adult normal subjects and during malnutrition, sepsis, and skeletal trauma. *Metabolism.* 1981;30(8):765–76.

7. Long CL, Haverberg LN, Young VR, Kinney JM, Munro HN, Geiger JW. Metabolism of 3-methylhistidine in man. *Metabolism.* 1975;24(8):929–35.

8. Neuhäuser M, Bergström J, Chao L, Holmström J, Nordlund L, Vinnars E, et al. Urinary excretion of 3-methylhistidine as an index of muscle protein catabolism in postoperative trauma: the effect of parenteral nutrition. *Metabolism.* 1980;29(12):1206–13.

9. Sander M, von Heymann C, von Dossow V, Spaethe C, Konertz WF, Jain U, et al. Increased interleukin-6 after cardiac surgery predicts infection. *Anesth Analg.*2006;102(6):1623–9.

10. Sodha NR, Sellke FW. The effect of statins on perioperative inflammation in cardiac and thoracic surgery. *J Thorac Cardiovasc Surg.* 2015;149(6):1495–1501.

11. Chambers MA, Moylan JS, Reid MB. Physical inactivity and muscle weakness in the critically ill. *Crit Care Med.* 2009:S337-46.

12. Iwatsu K, Yamada S, Iida Y, Sampei H, Kobayashi K, Kainuma M, et al. Feasibility of Neuromuscular Electrical Stimulation Immediately After Cardiovascular Surgery. *Arch Phys Med Rehabil.* 2015;96:63–8.

13. Haverberg LN, Deckelbaum L, Bilmazes C, Munro HN, Young VR. Myofibrillar protein turnover and urinary N-tau-methylhistidine output. Response to dietary supply of protein and energy. *Biochem J.* 1975;152(3):503–10.

14. Munro HN, Young VR. Urinary excretion of N gamma-methylihistidine (3-methylihistidine): a tool to study metabolic responses in relation to nutrient and hormonal status in health and disease of man. *Am J Clin Nutr.* 1978;31(9):1608–14.

15. Minkler PE, Ingalls ST, Griffin RL, Hoppel CL. Rapid high-performance liquid chromatography of 3-methylhistidine in human urine. *J Chromatogr.* 1987;413:33–42.

16. Quittan M, Wiesinger GF, Sturm B, Puig S, Mayr W, Sochor A, et al.

Improvement of thigh muscles by neuromuscular electrical stimulation in patients with refractory heart failure: a single-blind, randomized, controlled trial. *Am J Phys Med Rehabil .* 2001;80(3):206-14–6, 224.

17. Vivodtzev I, Pépin J-L, Vottero G, Mayer V, Porsin B, Lévy P, et al. Improvement in quadriceps strength and dyspnea in daily tasks after 1 month of electrical stimulation in severely deconditioned and malnourished COPD. *Chest.* 2006;129(6):1540–8.

18. Fess E. *Clinical Assessment Recommendations*. Moran, CA: American Society of Hand Therapists; 1981.

19. Haverberg LN, Omstedt PT, Munro HN, Young VR. Ntau-methylhistidine content of mixed proteins in various rat tissues. *Biochim Biophys Acta.* 1975;405(1):67–71.

20. Iida Y, Yamazaki T, Arima H, Kawabe T, Yamada S. Predictors of surgery-induced muscle proteolysis in patients undergoing cardiac surgery. *J Cardiol.* 2016 [Epub head of print].

21. Bouletreau P, Patricot MC, Saudin F, Guiraud M, Mathian B. Effects of intermittent electrical stimulations on muscle catabolism in

intensive care patients. *JPEN J Parenter Enteral Nutr.* 1987;11(6):552–5.

22. Strasser EM, Stättner S, Karner J, Klimpfinger M, Freynhofer M, Zaller V, et al. Neuromuscular electrical stimulation reduces skeletal muscle protein degradation and stimulates insulin-like growth factors in an age- and current-dependent manner: a randomized, controlled clinical trial in major abdominal surgical patients. *Ann Surg.* 2009;249(5):738–43.

23. Tiao G, Hobler S, Wang JJ, Meyer TA, Luchette FA, Fischer JE, et al. Sepsis is associated with increased mRNAs of the ubiquitin-proteasome proteolytic pathway in human skeletal muscle. *J Clin Invest.* 1997;99(2):163–8.

24. Hasselgren PO, Fischer JE. The ubiquitin-proteasome pathway: review of a novel intracellular mechanism of muscle protein breakdown during sepsis and other catabolic conditions. *Ann Surg.* 1997;225(3):307–16.

25. Neder J, Sword D, Ward S, Mackay E. Home based neuromuscular

electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). *Thorax.* 2002;57:333–337.

26. Harris S, LeMaitre JP, Mackenzie G, Fox KA, Denvir MA. A randomised study of home-based electrical stimulation of the legs and conventional bicycle exercise training for patients with chronic heart failure. *Eur Heart J.* 2003;24(9):871–8.

27. Bickel CS, Slade J, Mahoney E, Haddad F, Dudley GA, Adams GR. Time course of molecular responses of human skeletal muscle to acute bouts of resistance exercise. *J Appl Physiol.* 2005;98(2):482–8.

28. Gondin J, Guette M, Ballay Y, Martin A. Electromyostimulation training effects on neural drive and muscle architecture. *Med Sci Sports Exerc.* 2005;37(8):1291–9.

29. Hortobágyi T, Scott K, Lambert J, Hamilton G, Tracy J. Cross-education of muscle strength is greater with stimulated than voluntary contractions. *Motor Control.* 1999;3(2):205–19.

30. Huang L-P, Zhou S, Lu Z, Tian Q, Li X, Cao L-J, et al. Bilateral effect of

389 unilateral electroacupuncture on muscle strength. *J Altern*
390 *Complement Med.* 2007;13(5):539–46.

391 31. Routsi C, Gerovasili V, Vasileiadis I, Karatzanos E, Pitsolis T,
392 Tripodaki E, et al. Electrical muscle stimulation prevents critical
393 illness polyneuromyopathy: a randomized parallel intervention trial.
394 *Crit Care.* 2010;14(2):R74.

395

Tables

Table1. Patients' characteristics of NMES and non NMES group

	NMES n=61	non NMES n=41	*p*
Age, yrs	69 (62-74)	70 (65-75)	0.77
Female, n (%)	16 (26.2)	10 (24.4)	0.83
BMI, kg/m^2	23.3±3.5	23.4±3.5	0.90
Preoperative hemoglobin, g/dL	12.9 (11.9-14.1)	12.4 (11.5-13.5)	0.05
Preoperative Grip strength, kg	36 (29-41)	33 (27-41)	0.63
Preoperative KEIS, kg/Wt	0.42 (0.35-0.48)	0.39 (0.24-0.49)	0.26
Operative procedure			
Coronary artery bypass, n (%)	25 (40.9)	19 (46.3)	0.16
Valvular, n (%)	20 (32.8)	15 (36.6)	
Thoracic aorta, n (%)	10 (16.4)	1 (2.4)	
Combined, n (%)	6 (9.8)	6 (14.6)	
CPB time, min	169 (111-196)	178 (139-202)	0.13
Cross clamp time, min	108 (0-138)	127 (88-153)	<0.05
log IL-6, pg/dl	2.2±0.4	2.3±0.3	0.10
Days from surgery to initial mobilization, days	3 (2-3)	2 (2-3)	0.34

Data are expressed in mean ±SD or median (inter-quartile range).

NMES: neuromuscular electrical stimulation; BMI: body mass index; KEIS: knee extensor isometric strength; CPB time: cardiopulmonary bypass time; log IL-6: logarithmic interleukin-6

Figures

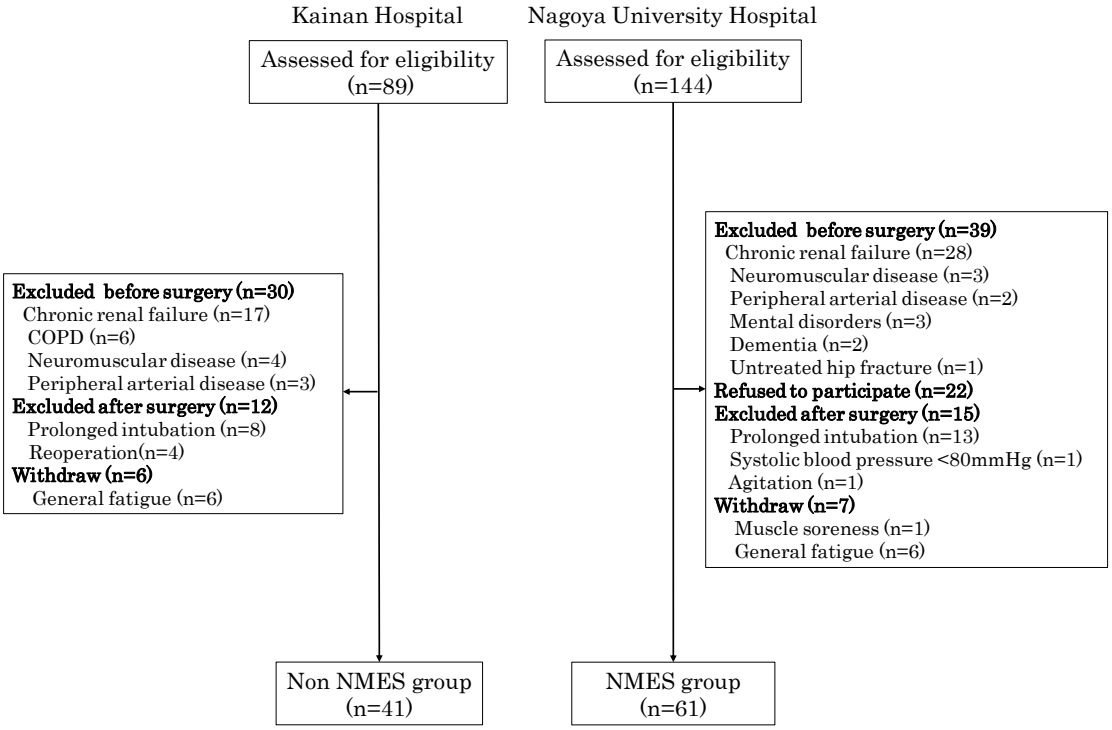


Figure1. Flow diagram of study participants

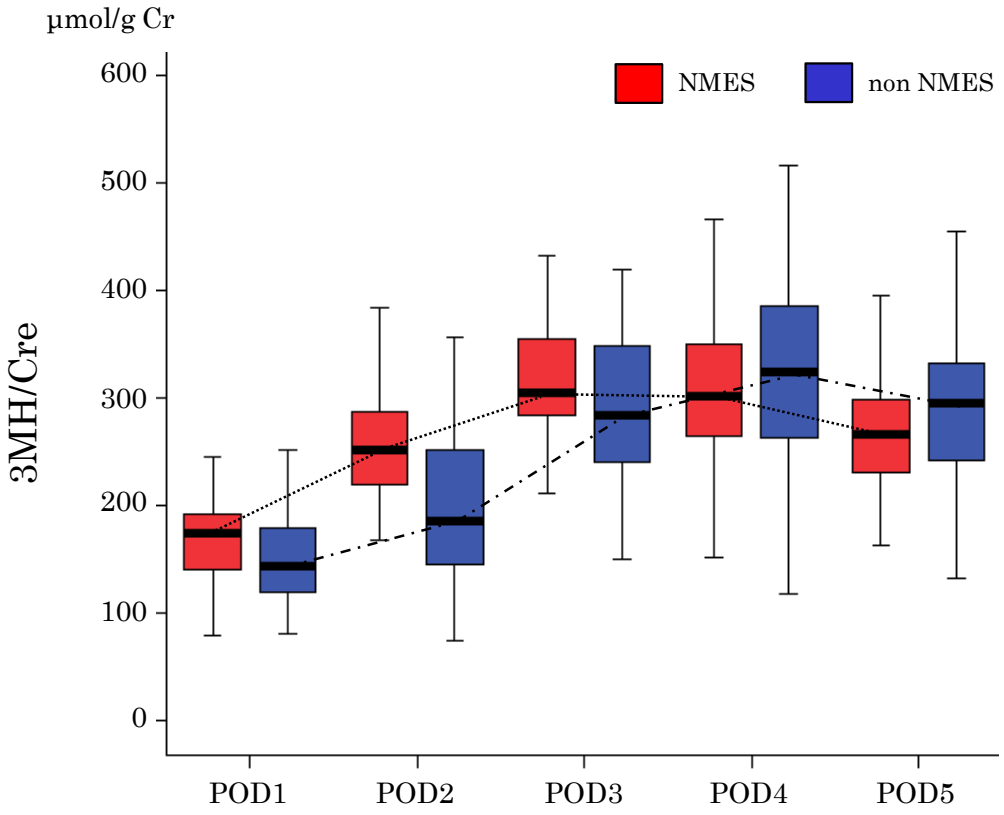


Figure2. Time trend of urinary 3-MH/Cre from POD1 to 5 in NMES (n=61) and non NMES (n=41) groups.

NMES; neuromuscular electrical stimulation; POD: postoperative day

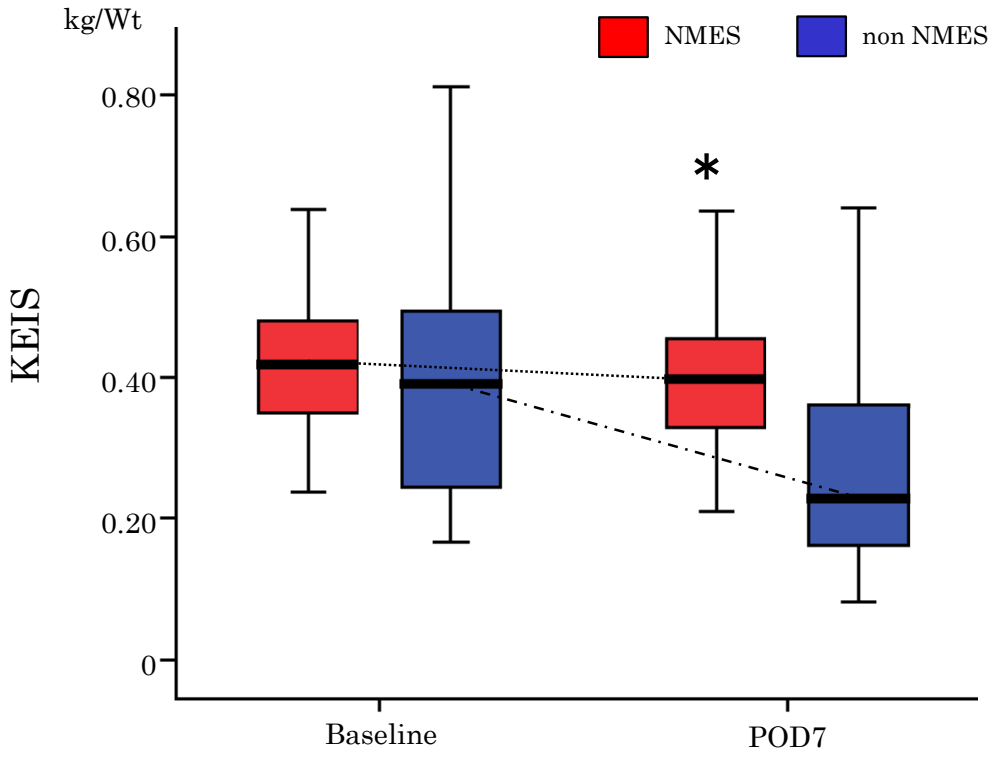


Figure3. KEIS at baseline and POD7 in NMES (n=61) and non NMES (n=41) groups

* Significant between-group difference ($p < 0.01$).

KEIS; knee extensor isometric strength, NMES; neuromuscular electrical stimulation; POD: postoperative day; Wt, weight

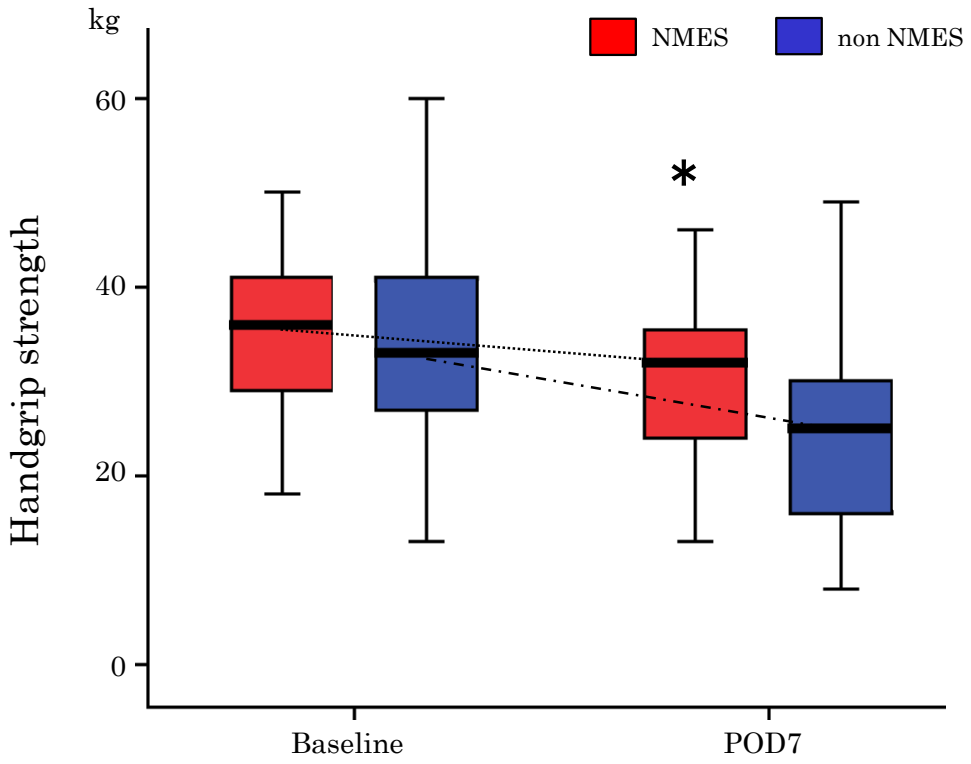


Figure4. Handgrip strength at baseline and POD7 in NMES (n=61) and non NMES (n=41) groups

* Significant between-group difference ($p < 0.01$)

NMES: neuromuscular electrical stimulation; POD: postoperative day

Appendices

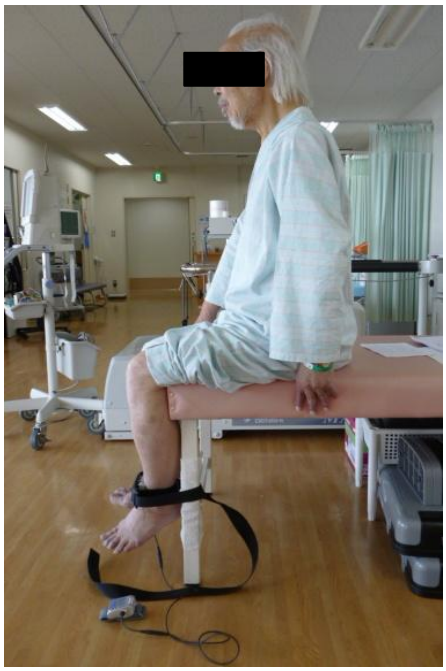
Appendix1. Supplemental Video: Neuromuscular electrical stimulation

Appendix2. Postoperative mobilization protocol form PODs 1 to 7 in each hospital

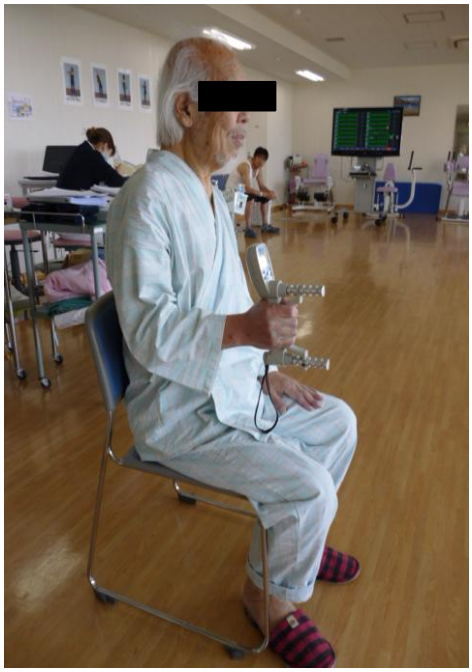
	NMES group	non NMES group
POD 1	sitting on the edge of the bed	sitting on the edge of the bed
POD 2	standing at bedside walking around the bed	standing at bedside walking around the bed
POD 3	walking in the corridor 50m	walking in the corridor 100m
POD 4	walking in the corridor 100m	walking 100m
POD 5	walking 200m	walking 300m
POD 6	walking 300m	walking 300m
POD 7	aerobic exercise using cycle ergometer	aerobic exercise using cycle ergometer

POD: postoperative day; NMES: neuromuscular electrical stimulation

Appendix3. Supplemental Figure: Measurement of muscle strength



Measurement of KEIS



Measurement of handgrip strength